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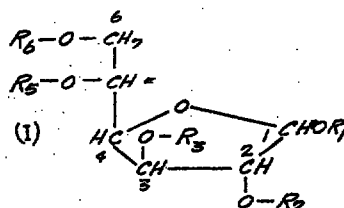


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(54) FURANOSIDES, PROCESS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

(71) We, CIBA GEIGY AG formerly Ciba Limited, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides D-glucofuranosides of the formula



(I)

in which R₁ represents a lower aliphatic hydrocarbon radical which may contain hydroxyl or lower alkoxy groups, or a cycloaliphatic hydrocarbon radical which may contain lower alkyl groups, or a benzyl radical whose phenyl ring may be substituted, R₂ represents a hydrogen atom or the acyl radical of an organic carboxylic acid, R₃ represents a hydrogen atom or a lower aliphatic hydrocarbon radical, and R₄ and R₅ each represents a benzyl radical whose phenyl ring may be substituted, with the proviso that when R₃ represents a lower aliphatic hydrocarbon radical, R₄ and R₅ together contain at least 3 carbon atoms, and salts of such compounds containing a salt-forming group.

The above compounds have the configuration of D-glucofuranose; the etherified hydroxyl group in the 1-position may have the α- or the β-configuration, and the compounds of this invention may be in the form of pure anomers or of mixtures of anomers.

The lower aliphatic hydrocarbon radical represented by R₁ is advantageously a lower alkyl group or a lower alkenyl group; these radicals, especially a lower alkyl group, may be substituted by one, two or more hydroxyl or lower alkoxy groups. Cycloaliphatic hydrocarbon radicals are especially cycloalkyl groups containing, for example, 3 to 8, preferably 5 or 6, carbon atoms in the ring, or cycloalkenyl groups containing, 5 to 8, preferably 5 or 6, carbon atoms in the ring; cycloaliphatic hydrocarbon radicals may be substituted by lower alkyl groups. Substituents of the phenyl ring in optionally substituted benzyl groups are, for example, lower alkyl groups etherified and esterified hydroxyl groups, such, for example, as lower alkoxy and lower alkylendioxy groups, halogen atoms, and "pseudohalogen" groups, such, for example, as trifluoromethyl groups.

An acyl radical represented by R₂ of an organic carboxylic acid is preferably the radical of an aliphatic, aromatic or araliphatic carboxylic acid, such, for example, as

a lower alkanecarboxylic or alkenecarboxylic acid, for example, acetic or propionic acid, and especially of a lower alkanedicarboxylic acid containing 2 to 7, preferably 3 to 6, carbon atoms, or of an equivalent lower alkene-dicarboxylic acid containing 4 to 7 carbon atoms; such acids are, for example, malonic, 2-methylsuccinic, glutaric, 3-methylglutaric, 3-ethylglutaric, adipic and pimelic acid and, advantageously succinic acid, and also maleic and fumaric acid.

A lower aliphatic hydrocarbon radical represented by R_3 is advantageously a lower alkyl or lower alkenyl radical.

A benzyl radical represented by R_5 or R_6 , which may be substituted in the phenyl nucleus, may be substituted by the groups and/or atoms mentioned above that may substitute the phenyl nucleus of R_1 .

The groups, radicals or compounds designated below and hereinafter as "lower" contain up to 7 carbon atoms. The number of carbon atoms preferred is up to 4.

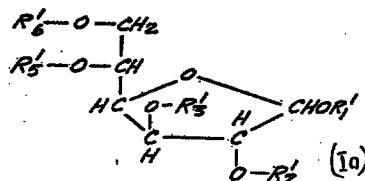
Lower alkyl radicals are, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, secondary butyl, tertiary butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, isohexyl, *n*-heptyl or isoheptyl radicals. Lower alkenyl radicals are, for example, allyl or methallyl or 2-butenyl radicals. The lower alkoxy groups occurring as substituents in such lower aliphatic hydrocarbon, especially lower alkyl, radicals are, for example methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *n*-pentoxy or *n*-hexoxy radicals. Lower aliphatic hydrocarbon radicals substituted by hydroxyl or lower alkoxy groups are advantageously hydroxy- or lower alkoxy-lower alkyl radicals, in which the hydroxyl or lower alkoxy groups are separated preferably by at least 2 carbon atoms from the oxygen atom that carries such a substituted lower aliphatic radical, such, for example, as 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-methoxyethyl, 2-ethoxyethyl, 2-methoxy-propyl, 3-methoxypropyl or 3-ethoxypropyl or hydroxy-methyl radicals.

Cycloalkyl radicals are preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals which may carry one or several lower alkyl groups, especially methyl groups, as substituents. Cycloalkenyl radicals are, for example, 2- or 3-cyclopentenyl, 2- or 3-cyclohexenyl or 2-, 3- or 4-cycloheptenyl radicals, optionally substituted as indicated above for the cycloalkyl radicals.

The phenyl nucleus of benzyl radicals may carry one, two or several substituents which may be identical or different. Halogen atoms are advantageously those having an atomic weight of 19 to 80, that is to say fluorine, chlorine or bromine atoms. Benzyl radicals monosubstituted in the nucleus carry a substituent preferably in the para-position.

The compounds of the invention possess useful pharmacological properties. More especially, they have an anti-inflammatory effect as can be shown in animal tests, for example, on the rat, by intraperitoneal administration of a dose from 0.30 to 0.3 g/kg. Thus, they show, for example, a stronger effect in the turpentine pleuritis test (performed in analogy to the test described by Spector in *J. Path. Bact.*, volume 72, page 367 [1956]) than known compounds of similar structure. Furthermore, as can be shown in animal tests, for example, on the guinea pig, they have antiallergic effects; compared with known compounds, they display on isolated smooth-muscle organs, a stronger antagonism towards histamine, serotonin, bradykinin and arachidonic acid peroxide. Furthermore, the activity of the compounds of the invention lasts much longer than that of known compounds having a similar activity spectrum. The compounds of the invention are, therefore, useful as anti-inflammatory, especially as anti-exudative or anti-edematous agents, or as anti-allergics, and are also valuable intermediates, for example, for the manufacture of other, especially pharmacologically active, compounds.

Especially useful anti-inflammatory properties are found in D-glucofuranosides of the formula

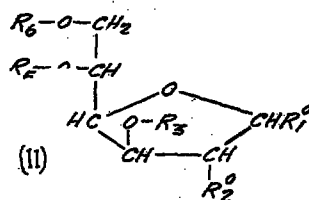


in which R'_1 represents a lower alkyl group, R'_2 represents a hydrogen atom or the acyl radical of a lower alkane-dicarboxylic acid, especially the succinyl radical, R'_3

represents a hydrogen atom or a lower alkyl or the allyl radical, and R_6' and R_6'' each represents a benzyl group which may contain, preferably in the para-position, a lower alkyl, especially methyl, radical or a halogen, especially a chlorine atom, with the proviso that, when R_3' represents a lower alkyl group, R_1' and R_3' together contain at least 3 carbon atoms, and salts, especially physiologically tolerable salts, such, for example, as physiologically tolerable ammonium, alkali metal or alkaline earth metal salts of compounds in which R_2' represents the acyl radical of a lower alkane-dicarboxylic acid, especially a succinyl radical.

Especially pronounced pharmacological properties of the kind mentioned above are found in lower alkyl-3-O- R_3'' -5,5-di-O-R-D-glucofuranosides, in which R_3'' represents a hydrogen atom or a lower alkyl group, and R represents a benzyl radical which may be substituted by halogen atoms, especially chlorine atoms, preferably in the 4-position, with the proviso that, when R_3'' stands for a lower alkyl radical, this radical together with the lower alkyl group of the substituent in the 1-position contains at least 3 carbon atoms, and their 2-O-succinyl compounds and their physiologically tolerable salts, for example, those of the kind referred to above, especially ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside, in the form of the mixture of anomers or of the pure anomers, and its 2-O-succinyl compound and its salts, especially of the kind mentioned above, which on intraperitoneal administration to the rat in a dose from 0.03 to 0.3 g/kg produce a pronounced anti-inflammatory effect of prolonged duration.

The compounds of this invention may be manufactured in known manner, for example, by reacting a D-glucofuranose of the formula



in which R_3 , R_6 and R_6' have their above meanings and in which R_1^0 represents a free hydroxyl group and R_2^0 a free hydroxyl group or an acyloxy group, in which acyl is the radical of an organic carboxylic acid, or R_1^0 and R_2^0 together stand for the grouping of the formula $-O-X-O-$, in which X represents an optionally substituted methylene group, with a compound of the formula R_1-OH (R_1 having its above meaning and being such that if R_3 represents a lower aliphatic carbon radical, R_1 and R_3 together contain at least 3 carbon atoms) in the presence of an acid and, if desired, saturating in a resulting compound an unsaturated lower aliphatic hydrocarbon radical and/or, if desired, converting in a resulting compound an acyloxy radical in the 2-position into a free hydroxyl group or another acyloxy group and/or esterifying a free hydroxyl group in the 2-position with an organic carboxylic acid.

The acyl radical of an organic carboxylic acid is, for example, a radical of one of the acids mentioned above.

A symbol X in the starting material of the formula II represents an unsubstituted, monosubstituted or preferably disubstituted methylene group. Substituents are advantageously unsubstituted or substituted monovalent or divalent aliphatic hydrocarbon radicals, preferably lower alkyl, for example, ethyl, *n*-propyl, isopropyl or *n*-butyl, especially methyl, radicals, or lower alkylene radicals containing 4 to 6 chain carbon atoms, such, for example, as 1,4-butylenes or 1,5-pentylene radicals. If desired, these hydrocarbon radicals may be substituted, for example, by lower alkyl, hydroxyl or lower alkoxy groups or halogen atoms, or aromatic groups, such, for example, as phenyl groups which themselves may be substituted, for example, by lower alkyl, hydroxyl or lower alkoxy groups or halogen atoms. Further substituents of the methylene group represented by X are, for example, aromatic radicals, such, for example, as phenyl groups, which may be substituted as indicated above, or free or functionally modified, such, for example, as esterified, carboxyl groups, for example, carbo-lower alkoxy, such, for example, as carbomethoxy or carbethoxy, groups.

An acid used in the reaction is a Lewis acid, especially an inorganic acid, such, for example, as a mineral acid, advantageously hydrochloric acid, but may also be hydrobromic or sulfuric acid, or an organic acid, such, for example, as an organic sulfonic acid, such as *p*-toluenesulfonic acid, or a mixture of acids, for example, a mixture of hydrochloric and acetic acid.

The reaction of a starting material of the formula II, in which R_3 , R_5 and R_6 have their above meanings and in which R_1° represents a free and R_2° a free or acylated hydroxyl group, with an alcohol of the formula $R_1\text{—OH}$ (R_1 having its above meaning) is preferably performed at a mineral acid concentration of 0.05N to 1N, more especially, of 0.1N to 0.5N.

The above reaction is preferably carried out in the presence of a diluent; among others, the alcoholic reagent of the formula $R_1\text{—OH}$ may at the same time also serve as such diluent. If desired, a mixture of solvents or diluents may be used.

The compounds of this invention may also be obtained, when a D-glucofuranose of the above formula II, in which R_3 , R_5 and R_6 have their above meanings and in which R_1° represents a reactive esterified hydroxyl group and R_2° represents an acyloxy radical, in which acyl is the acyl radical of an organic carboxylic acid, is reacted with a compound of the formula $R_1\text{—OH}$ in the presence of an acid acceptor; (R_1 having its above meaning and being such that if R_3 represents a lower aliphatic carbon radical R_1 and R_6 together contain at least 3 carbon atoms), and if desired, the optional steps are carried out.

A reactive, esterified hydroxyl group is advantageously a hydroxyl group esterified by a hydrohalic acid, so that R_1° is advantageously a halogen atom, especially a bromine atom.

An acid acceptor is, for example, a silver, lead or mercury salt or a corresponding oxide, or a tertiary base, or advantageously a metal derivative of a compound of the formula $R_1\text{—OH}$, such, for example, as a corresponding alkali metal, for example, sodium or potassium, salt or an alkaline earth metal, for example, magnesium, salt, or a silver compound.

The above reaction is preferably carried out in the presence of a solvent the alcoholic reagent may, if desired, be used as diluent.

In a compound of the present invention, an unsaturated lower aliphatic hydrocarbon radical, such, for example, as a lower alkenyl, for example, allyl, radical may be saturated, for example, by treatment with catalytically activated hydrogen, e.g. hydrogen in the presence of a palladium catalyst.

When R_2 in a compound of this invention represents an acyl radical, it may be replaced by hydrogen, for example, by treatment with an alkaline reagent, such, for example, as a hydroxide or carbonate of an alkali or alkaline earth metal, or with silver oxide, in an aqueous or alcoholic medium.

In a compound in which R_2 represents a hydrogen atom, the free hydroxyl group may be esterified by treatment with an acylating agent capable of introducing the acyl radical of an organic carboxylic acid in known manner. This reaction is preferably carried out on compounds in which R_3 represents a lower aliphatic hydrocarbon radical. Suitable acylating agents are acid derivatives (in the case of dicarboxylic acids, for example, their mono-acid derivatives), especially anhydrides (also inner anhydrides, such, for example, as corresponding ketenes), or halides, especially chlorides. Preferably, the reaction is carried out with an anhydride, for example, succinic anhydride, in the presence of an acid or basic catalyst, for example, pyridine. The reaction with a carboxylic acid halide, for example, a chloride, such, for example, as succinic acid monochloride, may be carried out in the presence of an acid-accepting condensing agent, such, for example, as a tertiary base or sodium acetate. If desired, a free hydroxyl group may be esterified with the aid of carboxylic acids in the presence of a suitable condensing agent, such, for example, as dicyclohexylcarbodiimide, or of a reactive ester of a carboxylic acid, such, for example, as an ester with N-hydroxyamino or N-hydroxyimino compounds, for example, N-hydroxysuccinimide.

Compounds containing an acyl radical represented by R_2 with salt-forming groups, for example, free carboxyl groups, are obtained according to the reaction conditions in the free form or as salts, which forms can be converted one into the other. Salts of compounds containing free carboxyl groups are, for example, metal salts, especially alkali metal salts, for example, sodium or potassium salts, or alkaline earth metal salts, for example, magnesium or calcium salts, or ammonium salts, for example, salts with ammonia or with organic bases, such, for example, as tri-lower alkylamines, for example, trimethylamine or triethylamine, especially the physiologically tolerable salts of the above kind. Such salts, especially the alkali metal salts of the compounds of the invention, are distinguished by their good solubility in water. Salts may also be used for purifying the free compounds. Salts are obtained, for example, by treating the free compounds with a hydroxide or carbonate of a metal or with ammonia or amines or with suitable ion exchange resins.

In view of the close relationship between the compounds of the invention in the free form and in the form of their salts, what has been said above and hereinafter with

reference to the free compounds or the salts concerns also the corresponding salts and free compounds, respectively, wherever possible and suitable.

The compounds of the invention may be in the form of pure α - or β -anomers or of mixtures of anomers. The latter can be resolved into the two pure anomers on the basis of the physico-chemical differences of the constituents, for example, by chromatographic separation, e.g. thin layer chromatography, or by any other suitable separation procedure. Preferably, the more physiologically active of the two anomers is isolated.

The processes described above are performed by known methods, in the absence or preferably presence of diluents or solvents, if necessary with cooling or heating, under increased pressure and/or in the atmosphere of an inert gas, such as nitrogen.

The invention includes also those modifications of the process in which a starting material is formed under the reaction conditions or is used in form of a reactive derivative thereof.

Preferred starting materials are those which give the products previously designated as being especially useful.

The starting materials are known or, insofar as they are new, they can be manufactured in known manner. Thus, for example, they are obtained, when in a D-glucofuranose the hydroxyl groups in the 1- and 2-positions and, if desired, in the 5- and 6-positions, are protected by introducing protective groups, for example, the group represented by X, which is especially an isopropylidene or a benzylidene group. The hydroxyl group in the 3-position can then be etherified by treatment with a reactive ester of a compound of the formula R_3 -OH, for example, a lower aliphatic R_3 -halide, e.g. R_3 -chloride or R_3 -bromide, and a corresponding R_3 -sulfonyloxy compound (R_3 having its above meaning), in the presence of a basic reagent, such, for example, as an alkali metal hydroxide, for example, sodium or potassium hydroxide, or of an alkali metal carbonate, for example, sodium or potassium carbonate. This etherification with a reactive ester of a compound of the formula R_3 -OH may be performed under suitable conditions, for example, in the presence of silver oxide or of an alkali metal, for example, potassium, carbonate, also on the 3,5,6-trihydroxy compound without simultaneous etherification of the hydroxyl groups in the 5- and 6-positions.

In an intermediate with protected hydroxyl groups in the 5- and 6-positions obtained in this manner these groups may be selectively liberated, that is without liberating the hydroxyl groups in the 1- and 2-positions, for example, by treatment with an acid, such, for example, as 60% aqueous acetic acid (for example at 35°C) or aqueous ethanolic hydrochloric acid, and then themselves etherified by optionally substituted benzyl groups, for example, with the use of reactive esterified, optionally substituted benzyl alcohols, such, for example, as the corresponding halides, for example, chlorides or bromides, and sulfonyloxy, e.g. *p*-toluenesulfonyloxy, compounds, in the presence of basic reagents, such, for example, as an alkali metal hydroxide, for example, potassium hydroxide. If desired, this process may be carried out stepwise, since the primary hydroxyl group in the 6-position can be etherified before the hydroxyl group in the 5-position, for example, on treatment with an approximately equivalent amount of a reactive ester of a compound of the formula R_6 -OH (R_6 having its above meaning) in the presence of an approximately equivalent quantity of an alkali metal hydroxide or in the presence of silver oxide.

In a 5,6-dihydroxy compound containing in the 3-position a free or preferably etherified hydroxyl group, the hydroxyl group in the 6-position may be selectively esterified, for example, by treatment with a suitable organic sulfonyl halide, such, for example, as *p*-toluenesulfonyl chloride, and upon treatment with a suitable basic reagent, such, for example, as an alkali metal lower alkoxide, such, for example, as sodium ethoxide, the 5,6-epoxy compound may be formed. Splitting of the epoxide by means of an alcohol of the formula R_5 -OH in the presence of a transesterifying catalyst, for example, an alkali metal, such, for example, as sodium, compound of an alcohol of the formula R_5 -OH, the 5-hydroxy-6- R_5 -O-compound is obtained (R_5 having its above meaning); in this compound, the free hydroxyl group in the 5-position can be selectively etherified, for instance, by treatment with a reactive ester of a compound of the formula R_5 -OH (R_5 having its above meaning) in the presence of a basic reagent, for example, one of those described above.

In the starting materials obtainable by the above procedures, in which R_3 preferably represents a lower aliphatic radical, the protective group for the two hydroxyl groups in positions 1 and 2 may be eliminated, for example, by treatment with an aqueous acid, such, for example, as hydrochloric acid. The two hydroxyl groups may then be esterified by treatment with a suitable derivative of an organic carboxylic acid, such, for example, as acetic acid, for example, an anhydride thereof, e.g. acetic anhydride, to form a 1,2-bis-O-acyl-compound, especially 1,2-bis-O-acetyl-compound.

On reaction, for example, with bromine in glacial acetic acid, a 2-O-acyl, e.g. 2-O-acetyl, compound containing a reactive, esterified hydroxyl group, e.g. a bromine atom, in the 1-position is formed, which may be used as starting material.

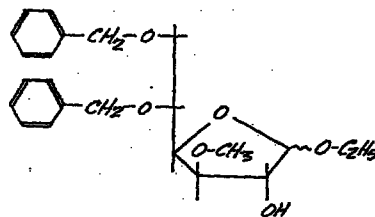
At any suitable stage of the above process for the manufacture of the starting materials, a hydroxyl group in the 3-position etherified with a suitable 2-alkenyl radical, such for example, as the allyl radical, may be liberated, for example, by rearrangement of the double bond by treatment with an appropriate base, such, for example, as an alkali metal, for example, potassium tertiary butoxide, preferably in a suitable solvent, for example, dimethylsulfoxide, and oxidative-hydrolytic replacement by hydrogen of the 1-lower alkenyl, such, for example, as 1-propenyl group, for example, by treatment with potassium permanganate, preferably in a basic medium, such, for example, as an ethanolic alkali metal hydroxide, for example, potassium hydroxide, solution.

The compounds of the invention or their physiologically tolerable salts may be used as medicaments, for example, in form of pharmaceutical preparations containing them in conjunction or admixture with an organic or inorganic, solid or liquid pharmaceutical carriers suitable, for example, for enteral or parenteral or topical administration. Suitable carriers are substances that are inert towards the compounds of the invention, such, for example, as water, gelatin, sugars, for example, lactose, glucose or fructose, starches, such, for example, as corn, wheat or rice starch, stearic acid or physiologically tolerable salts thereof, such, for example, as calcium or magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, polyalkyleneglycols, propyleneglycol or other known medicinal carriers. The pharmaceutical preparations may be in the solid form, for example, as tablets, dragées or capsules, or in liquid form, e.g. as solutions, suspensions or emulsions. They may be sterilized and/or may contain auxiliary substances, such, for example, as preserving, stabilizing, wetting or emulsifying agents, physiologically tolerable salts for regulating the osmotic pressure or buffers. They may also contain further therapeutically useful substances. The preparations may be formulated by conventional methods.

The following Examples illustrate the invention; temperatures are given in degrees Centigrade.

EXAMPLE 1

A solution of 149 g of 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-benzyl- α -D-glucufuranose in 3200 ml of absolute ethanol is mixed at 10° with 412 ml of a 7.75N ethanolic solution of hydrogen chloride. The reaction mixture is kept for 17 hours at room temperature, then cooled to 0—5° and neutralized with a 10N aqueous sodium hydroxide solution; the bulk of ethanol is then distilled off under reduced pressure at 40°, and the residue is extracted with chloroform. The chloroform phase is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled, to yield at 180°/0.02 mm. Hg. ethyl-3-O-methyl-5,6-di-O-benzyl-D-glucufuranoside of the formula

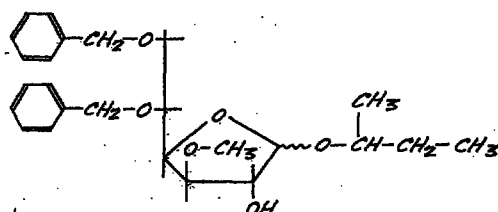


as a faintly yellowish oil; $[\alpha]_D^{20} = -31^\circ \pm 1^\circ$ ($c=1$ in chloroform). The anomer mixture is resolved into the pure anomers by thin-layer chromatography, eluting with an 85:15-mixture of chloroform and ethyl acetate, on silica gel (RF 254, of Messrs. Merck, Darmstadt). The α -anomer has an R_f value of 0.45; $[\alpha]_D^{20} = +34 \pm 1^\circ$ ($c=1$ in chloroform); the β -anomer an R_f value of 0.23; $[\alpha]_D^{20} = -61^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 2

A solution of 17.4 g of 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-benzyl- α -D-glucufuranose in 433 ml of a 1N solution of hydrogen chloride in *sec*-butanol is kept for 17 hours at room temperature then neutralized at 0—5° with a 10N aqueous sodium

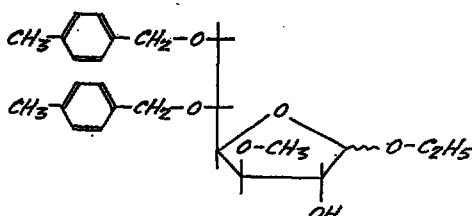
hydroxide solution; the bulk of *sec.*-butanol is distilled off under reduced pressure. The residue is extracted with chloroform and the chloroform extracts are washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under vacuum. The residue is distilled and yields at 200°/0.05 mm Hg *sec.*-butyl-3-O-methyl-5,6-di-O-benzyl-D-glucofuranoside of the formula



as a faintly yellowish oil; $[\alpha]_D^{20} = -24^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 3

A solution of 12.8 g of 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-(4-methylbenzyl)- α -D-glucofuranose in 298 ml of a 1N ethanolic solution of hydrogen chloride is kept for 17 hours at room temperature, then neutralized at 0–5°C with a 10N aqueous sodium hydroxide solution. The bulk of ethanol is distilled off under reduced pressure, and the residue is extracted with chloroform. The chloroform extracts are washed with aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under vacuum. The residue is distilled and yields at 195°/0.03 mm Hg ethyl-3-O-methyl-5,6-di-O-(4-methylbenzyl)-D-glucofuranoside of the formula



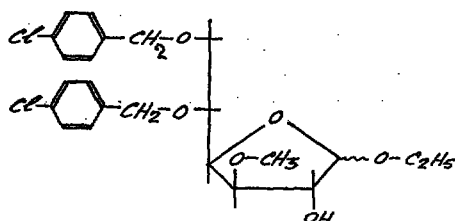
as a faintly yellowish oil; $[\alpha]_D^{20} = -14^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material used above may be prepared as follows:

A solution of 23.4 g of 1,2-O-isopropylidene-3-O-methyl- α -D-glucofuranose in 50 ml of absolute dioxan is mixed with 71.5 g of powdered potassium hydroxide. In the course of 30 minutes, 93.8 g of 4-methylbenzylchloride are added dropwise while stirring, and the reaction mixture is allowed to react for 5 hours at 80°. The excess 4-methylbenzyl chloride is distilled off with steam, the residue is allowed to cool and is then extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at 205°/0.02 mm Hg 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-(4-methylbenzyl)- α -D-glucofuranose as a faintly yellowish oil; $[\alpha]_D^{20} = -30^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 4

A solution of 11 g of 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucofuranose in 300 ml of a 1N solution of hydrogen chloride in ethanol is kept for 20 hours at room temperature and then neutralized at 0 to 5° with a 10N aqueous sodium hydroxide solution. The bulk of ethanol is distilled off under reduced pressure and the residue is extracted with chloroform; the chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under vacuum; the residue is distilled to yield at 190°/0.01 mm Hg ethyl-3-O-methyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside of the formula



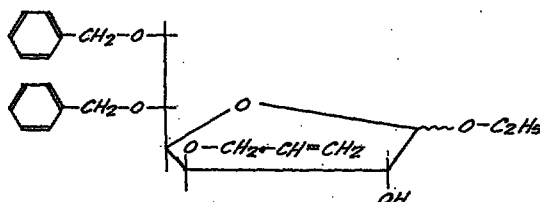
as a faintly yellowish oil; $[\alpha]_D^{20} = -14^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material used above may be prepared as follows:

A solution of 42 g of 1,2-O-isopropylidene-3-O-methyl- α -D-glucopyranose in 150 ml of absoluten dioxan is mixed with 128 g of powdered potassium hydroxide. In the course of 30 minutes, 192 g of 4-chlorobenzyl chloride are added dropwise while stirring and the reaction mixture is allowed to react for 5 hours at 80° . The excess 4-chlorobenzyl chloride is distilled off with steam, the residue is allowed to cool and is then extracted with chloroform. The chloroform solution is dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $235^\circ/0.02$ mm Hg 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucopyranose as a faintly yellowish oil; $[\alpha]_D^{20} = -22^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 5

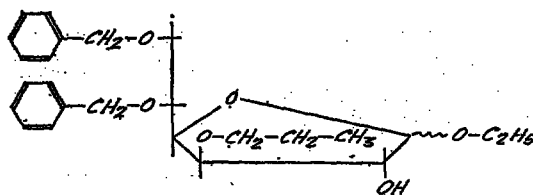
A solution of 12.75 g of 1,2-O-isopropylidene-3-O-allyl-5,6-di-O-benzyl- α -D-glucopyranose in 298 ml of a 1N ethanolic solution of hydrogen chloride is kept for 17 hours at room temperature and then neutralized at 0° to 5° with a 10N aqueous sodium hydroxide solution. The bulk of ethanol is distilled off under reduced pressure and the residue is extracted with chloroform. The chloroform extract is washed with a saturated sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $200^\circ/0.03$ mm Hg ethyl 3-O-allyl-5,6-di-O-benzyl-D-glucopyranoside of the formula



as a faintly yellowish oil; $[\alpha]_D^{20} = -18^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 6

A solution of 46 g of 1,2-O-isopropylidene-3-O-n-propyl-5,6-di-O-benzyl- α -D-glucopyranose in 1060 ml of a 1N ethanolic solution of hydrogen chloride is kept for 17 hours at room temperature, then neutralized at 0° to 5° with a 10N solution of sodium hydroxide. The bulk of ethanol is distilled off at 40° under reduced pressure and the residue extracted with chloroform. The chloroform phase is washed with aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $220^\circ/0.03$ mm Hg ethyl 3-O-n-propyl-5,6-di-O-benzyl-D-glucopyranoside of the formula



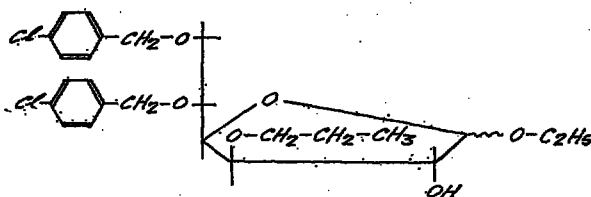
as a faintly yellowish oil; $[\alpha]_D^{20} = -24^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material used may be prepared as follows:

A solution of 82 g of 1,2-O-isopropylidene-3-O-allyl- α -D-glucufuranose in 800 ml of ethanol is hydrogenated in the presence of 1 g of a 10%-palladium-on-carbon catalyst. The catalyst is then filtered off, the filtrate is evaporated and the residue is degassed in a high vacuum. A solution of 38.9 of the resulting 1,2-O-isopropylidene-3-O-*n*-propyl- α -D-glucufuranose; $[\alpha]_D^{20} = -49^\circ \pm 1^\circ$ ($c=1$ in chloroform); in 150 ml of absolute dioxan is mixed with 107 g of powdered potassium hydroxide and, within 30 minutes, 114 ml of benzyl chloride are added dropwise while stirring. The reaction mixture is allowed to react for 5 hours at 80° , the excess benzyl chloride is distilled off with steam and the residue, after cooling, is extracted with chloroform. The organic extract is washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $190^\circ/0.015$ mm Hg 1,2-O-isopropylidene-3-O-*n*-propyl-5,6-di-O-benzyl- α -D-glucufuranose as a colorless oil; $[\alpha]_D^{20} = -30^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 7

A solution of 40 g of 1,2-O-isopropylidene-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucufuranose in 900 ml of a 1N ethanolic solution of hydrogen chloride is kept for 17 hours at room temperature, cooled to 0° — 5° and neutralized with a 10N aqueous sodium hydroxide solution; the bulk of ethanol is distilled off under reduced pressure and the residue is extracted with chloroform. The chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure; the residue is distilled under a high vacuum to yield at $195^\circ/0.01$ mm Hg ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside of the formula



as a faintly yellowish oil; $[\alpha]_D^{20} = -17^\circ \pm 1^\circ$ ($c=1$ in chloroform).

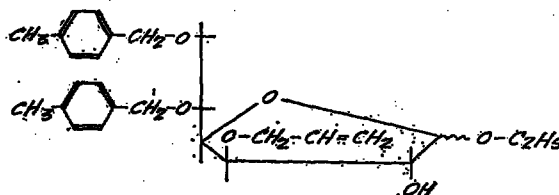
The resulting anomer mixture is resolved into the pure anomers by thin-layer chromatography on silica gel (RF 254, of Messrs. Merck, Darmstadt) and elution with an 85:15-mixture of chloroform and ethyl acetate. The α -anomer has an R_f value of 0.50; $[\alpha]_D^{20} = +24^\circ \pm 1^\circ$ ($c=1$ in chloroform); and the β -anomer an R_f value of 0.24; $[\alpha]_D^{20} = -45^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material used above may be prepared as follows:

A solution of 32 g of 1,2-O-isopropylidene-3-O-*n*-propyl- α -D-glucufuranose in 100 ml of absolute dioxan is mixed with 87.5 g of powdered potassium hydroxide, and within 30 minutes a solution of 131 g of 4-chlorobenzyl chloride in 50 ml of absolute dioxan is added dropwise while stirring; the reaction mixture is allowed to react for 5 hours at 80° . The excess 4-chlorobenzyl chloride is distilled off with steam and, after cooling, the residue is extracted with chloroform. The organic extract is washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $230^\circ/0.015$ mm Hg 1,2-O-isopropylidene-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucufuranose as a faintly yellowish oil; $[\alpha]_D^{20} = -22^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 8

A solution of 24.4 g of 1,2-O-isopropylidene-3-O-allyl-5,6-di-O-(4-methylbenzyl)- α -D-glucufuranose in 600 ml of a 1N ethanolic hydrogen chloride solution is kept for 17 hours at room temperature, then cooled to 0° — 5° and neutralized with a 10N aqueous sodium hydroxide solution. The bulk of ethanol is distilled off at 40° under reduced pressure and the residue is extracted with chloroform. The chloroform phase is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled under a high vacuum and yields at $215^\circ/0.02$ mm Hg ethyl-3-O-allyl-5,6-di-O-(4-methylbenzyl)-D-glucufuranoside of the formula



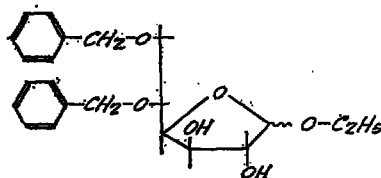
as a faintly yellowish oil; $[\alpha]_D^{20} = -10^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material used above may be prepared as follows:

A solution of 20 g of 1,2-O-isopropylidene-3-O-allyl- α -D-glucopyranose in 39 ml of absolute dioxane is mixed with 55 g of powdered potassium hydroxide. While stirring, 72 g of 4-methylbenzyl chloride are dropped in within 30 minutes and the reaction mixture is allowed to react for 5 hours at 80° . The excess 4-methylbenzyl chloride is distilled off with steam; the cooled residue is extracted with chloroform, the organic solution washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $200^\circ/0.015$ mm Hg 1,2-O-isopropylidene-3-O-allyl-5,6-di-O-(4-methylbenzyl)- α -D-glucopyranose as a faintly yellowish oil.

EXAMPLE 9

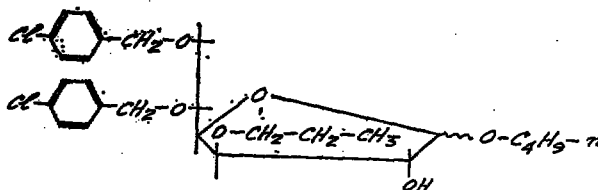
A solution of 3.5 g of 1,2-O-isopropylidene-5,6-di-O-benzyl- α -D-glucopyranose in 90 ml of a 1N ethanolic hydrogen chloride solution is kept for 17 hours at room temperature, cooled to 0° — 5° and neutralized with a 10N aqueous sodium hydroxide solution. The bulk of ethanol is distilled off at 40°C under reduced pressure and the residue is extracted with chloroform. The chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at $215^\circ/0.02$ mm Hg ethyl-5,6-di-O-benzyl-D-glucopyranoside of the formula



as a faintly yellowish oil; $[\alpha]_D^{20} = -17^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 10

A total of 20 g of 1,2-O-isopropylidene-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucopyranose is dissolved at 10° in 500 ml of a 1N solution of hydrogen chloride in *n*-butanol. The reaction mixture is kept for 17 hours at room temperature, then cooled to 0° — 5° and neutralized with a 10N aqueous sodium hydroxide solution. The bulk of *n*-butanol is distilled off under reduced pressure and the residue is extracted with chloroform. The chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is freed from residual solvent at 40° under a high vacuum, to yield *n*-butyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucopyranoside of the formula

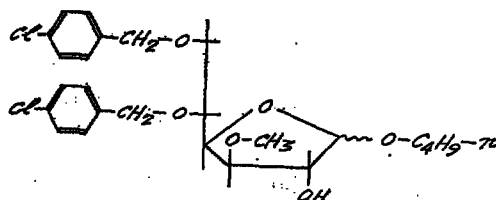


as a faintly yellowish oil; $[\alpha]_D^{20} = -21^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 11

A solution of 20 g of 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucopyranose in 500 ml of a 1N solution of hydrogen chloride in *n*-butanol is kept for 17 hours at room temperature and then neutralized with a 10N aqueous sodium

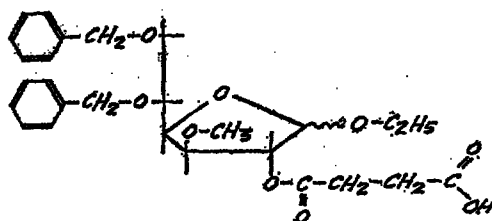
hydroxide solution at 0°—5°. The bulk of *n*-butanol is distilled off under reduced pressure, the residue is extracted with chloroform and the chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is freed from residual solvent at 40° under a high vacuum and yields *n*-butyl-3-O-methyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside of the formula



as a faintly yellowish oil; $[\alpha]_D^{20} = -20^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 12

A solution of 15 g of ethyl-3-O-methyl-5,6-di-O-benzyl-D-glucufuranoside in 30 ml of absolute pyridine is mixed with 4.1 g of finely powdered succinic anhydride, and the reaction mixture is heated for 28 hours at 70° while stirring and with the exclusion of moisture, then evaporated at 55° under reduced pressure. The residue is mixed with 45 ml of ice water and agitated for 5 minutes. The reaction mixture is extracted with ether; the ether solution is washed five times with 50 ml portions each of ice-cooled 2N hydrochloric acid and 50 ml each of ice water, dried over sodium sulfate and evaporated under reduced pressure. The residue is freed from residual solvent at 20° under a high vacuum and yields ethyl-2-O-(β -carboxypropionyl)-3-O-methyl-5,6-di-O-benzyl-D-glucufuranoside of the formula



as a thick oil.

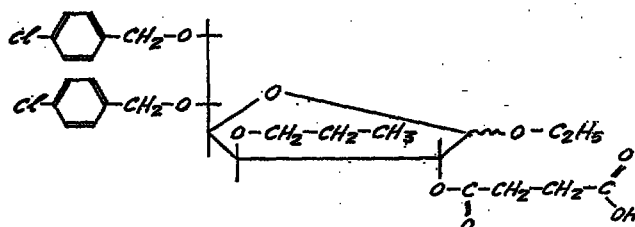
A solution of the above compound in an excess of a 1N solution of sodium hydroxide in aqueous ethanol is allowed to stand for a short time, whereupon the ester is quantitatively hydrolyzed. The resulting ethyl-3-O-methyl-5,6-di-O-benzyl-D-glucufuranoside can be characterized by thin-layer chromatography. The α -anomer has an R_f value of 0.45; $[\alpha]_D^{20} = +34^\circ \pm 1^\circ$ ($c=1$ in chloroform); and the β -anomer an R_f value of 0.23; $[\alpha]_D^{20} = -61^\circ \pm 1^\circ$ ($c=1$ in chloroform).

A solution of the product in ether is agitated with the theoretical quantity of an aqueous sodium bicarbonate solution. The ether is evaporated under reduced pressure and the residue is diluted with water until a clear solution is formed which is lyophilized. Upon diluting the lyophilizate with water, an at least 10% aqueous solution of the resulting sodium salt of ethyl-2-O-(β -carboxypropionyl)-3-O-methyl-5,6-di-O-benzyl-D-glucufuranoside can be prepared.

EXAMPLE 13

A solution of 2.75 g of succinic anhydride in 20 ml of absolute pyridine is mixed with a solution of 10 g of ethyl-3-O-n-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside in 20 ml of absolute pyridine; the reaction mixture is heated for 48 hours at 70° with the exclusion of moisture, and then evaporated at 55° under reduced pressure. The residue is mixed with 45 ml of ice water and agitated for 5 minutes, then extracted with ether. The ether phase is washed five times with 50 ml each of ice water, dried over sodium sulfate and evaporated under reduced pressure. The residue

is freed from residual solvent under a high vacuum and yields ethyl-2-O-(β -carboxypropionyl)-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside of the formula



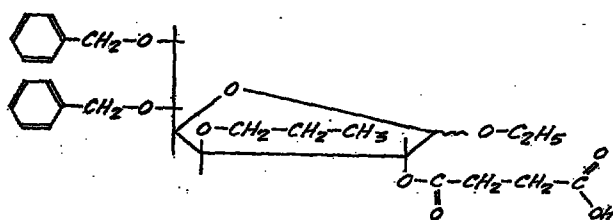
as a thick oil.

A solution of this compound in an excess of a 1N sodium hydroxide solution in aqueous ethanol is allowed to stand for a short time, whereupon the ester is quantitatively hydrolyzed. The resulting ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside can be characterized by thin-layer chromatography. The α -anomer has an R_f value of 0.50; $[\alpha]_D^{20} = +24^\circ \pm 1^\circ$ ($c=1$ in chloroform); and the β -anomer an R_f value of 0.24; $[\alpha]_D^{20} = -45^\circ \pm 1^\circ$ ($c=1$ in chloroform).

A solution of the product in ether is mixed with the theoretical quantity of sodium bicarbonate in water and freed from ether at 20° under reduced pressure. The residue is diluted with water until a clear solution is formed (9.5%), which can be lyophilized to yield the sodium salt of ethyl-2-O-(β -carboxypropionyl)-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside as a thick oil.

EXAMPLE 14

A solution of 2.55 g of succinic anhydride in 20 ml of absolute pyridine is mixed with a solution of 10 g of ethyl-3-O-*n*-propyl-5,6-di-O-benzyl-D-glucufuranoside and heated for 48 hours at 70° , then evaporated under reduced pressure at 55° . The residue is stirred for 30 minutes with 45 ml of ice water, then extracted with ether and the ether solution is washed five times with 50 ml each of ice-cooled 2N hydrochloric acid and 50 ml each of ice water, dried over sodium sulfate and evaporated under reduced pressure. The residue is freed from residual solvent under a high vacuum to yield ethyl-2-O-(β -carboxypropionyl)-3-O-*n*-propyl-5,6-di-O-benzyl-D-glucufuranoside of the formula



as a thick oil.

A solution of the above compound in an excess of a 1N solution of sodium hydroxide in aqueous ethanol is allowed to stand for a short time, whereupon the ester is quantitatively hydrolyzed. The ethanol is evaporated, the residue is extracted with methylene chloride and the extract is evaporated to yield ethyl-3-O-*n*-propyl-5,6-di-O-benzyl-D-glucufuranoside which is obtained as a faintly yellowish oil at $220^\circ/0.03$ mm Hg on distillation of the residue; $[\alpha]_D^{20} = -24^\circ \pm 1^\circ$ ($c=1$ in chloroform).

A solution of the product in ether is mixed with the theoretical quantity of sodium bicarbonate in water; the mixture is freed from ether at 40° under reduced pressure. The aqueous solution is lyophilized to yield the sodium salt of ethyl-2-O-(β -carboxypropionyl)-3-O-*n*-propyl-5,6-di-O-benzyl-D-glucufuranoside as a thick oil, which is soluble in water up to a concentration of 25%.

EXAMPLE 15

While cooling with ice, 5 ml of a 33% solution of hydrogen bromide in glacial acetic acid are added to 2.4 g of 1,2-di-O-acetyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose and the mixture is kept for 2-1/2 hours at room tempera-

ture, then poured into ice water and extracted with chloroform. The organic extract is washed with ice water and an ice-cold aqueous solution of sodium bicarbonate, dried over sodium sulfate and evaporated under reduced pressure at a bath temperature of 30–40°.

The residue, which contains 2-O-acetyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranosyl bromide, is mixed with 50 ml of a 1N ethanolic solution of sodium ethoxide and kept for 16 hours at room temperature, then neutralized with 2N aqueous acetic acid and extracted with chloroform. The organic extract is washed with ice water and an ice-cold concentrated aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated in a water-jet vacuum. The residue is distilled under a high vacuum, to yield at 195°/0.01 mm Hg ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside as a faintly yellowish oil; $[\alpha]_D^{20} = -17^\circ \pm 1^\circ$ ($c=1$ in chloroform).

The starting material may be prepared as follows:

A suspension of 5 g of 1,2-O-isopropylidene-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)- α -D-glucufuranose in a mixture of 35 ml of glacial acetic acid and 17.5 ml of 1N aqueous sulfuric acid is heated for 30 minutes at an internal temperature of 80° while being vigorously stirred under an atmosphere of nitrogen. The reaction mixture is then cooled to 10°, adjusted to a pH value of 2–3 with a 2N aqueous sodium hydroxide solution and evaporated at a bath temperature of 35°. The concentrate is extracted with ether, and the organic phase is washed with a saturated aqueous sodium bicarbonate solution and with water until the washings are neutral, dried over magnesium sulfate and evaporated. The residue is 3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose, with an R_f value of 0.12 in the thin-layer chromatogram on silica gel in the system chloroform: ethyl acetate (85:15). It melts at 60° after recrystallization from a 1:3-mixture of toluene and hexane and cooling to –17°.

3-O-*n*-Propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose is also obtained, when 15 g of ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside is treated with 600 ml of glacial acetic acid and 600 ml of water; the mixture is heated for 16 hours at 70°, the excess acetic acid is distilled off, the aqueous residue is extracted with ether and the ether solution is worked up as described above.

A solution of 12.5 g of 3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose in 13 ml of absolute pyridine is cooled, mixed with 13 ml of acetic anhydride and kept for 16 hours at room temperature, then diluted with 12 ml of water while being cooled. The aqueous layer is decanted from the oil which has settled out and the latter is taken up in ether. The organic phase is agitated with 2N hydrochloric acid, washed with water, dried over magnesium sulfate and evaporated. The residue is distilled and yields at 240°/0.05 mm the desired 1,2-di-O-acetyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose as a faintly yellowish oil.

EXAMPLE 16

A solution of 2.1 g of 3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranose in 25 ml of absolute ethanol containing 0.156 g of hydrogen chloride gas is allowed to stand at room temperature for 1 hour under an atmosphere of nitrogen, then, while being cooled, adjusted to a pH value of 7–7.5 with 30% aqueous sodium hydroxide solution and filtered; the filter residue is washed with ethanol. The combined filtrates are concentrated to half the volume at 30° under reduced pressure and diluted with water. The oily precipitate is separated and distilled under a high vacuum to yield at 195°/0.01 mm Hg ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside as a faintly yellowish oil; $[\alpha]_D^{20} = -17^\circ \pm 1^\circ$ ($c=1$ in chloroform).

EXAMPLE 17

Capsules, each containing 0.2 g of active substance, may be manufactured as follows (for 10000 capsules):

Ingredients

Ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside
absolute ethanol

2000 g
200 g

Ethyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucufuranoside is mixed with the ethanol and the mixture filled into soft gelatin capsules on a suitable encapsulating machine.



* C L M S *

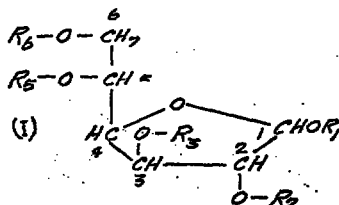
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1,240,169

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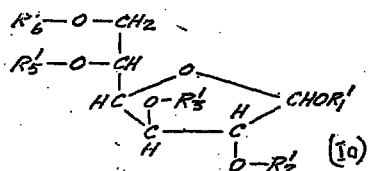
WHAT WE CLAIM IS:—

1. A D-glucofuranoside of the formula



wherein R_1 represents a lower aliphatic hydrocarbon radical which optionally carries hydroxyl or lower alkoxy groups, a cycloaliphatic hydrocarbon radical which optionally carries lower alkyl groups, or a benzyl radical which is optionally substituted in the phenyl ring, R_2 represents a hydrogen atom or the acyl radical of an organic carboxylic acid, R_3 represents a hydrogen atom or a lower aliphatic hydrocarbon radical, and R_4 and R_5 each represents a benzyl radical which is optionally substituted in the phenyl ring, with the proviso that if R_3 represents a lower aliphatic hydrocarbon radical, the groups represented by R_1 and R_3 together contain at least 3 carbon atoms.

2. A compound of the formula



wherein R_1' represents a lower alkyl radical, R_2' denotes a hydrogen atom or the acyl radical of a lower alkanedicarboxylic acid, R_3' represents a hydrogen atom, a lower alkyl radical or the allyl radical, and R_4' and R_5' each represents a benzyl group which optionally carries a lower alkyl radical or a halogen atom, with the proviso that if R_3' represents a lower alkyl radical, R_1' and R_3' together contain at least 3 carbon atoms.

3. A compound of formula Ia as claimed in claim 2, wherein R_1' and R_3' have the significance given in claim 2, R_2' represents a hydrogen atom or the succinyl radical and R_4' and R_5' each represents a benzyl group which optionally carries a methyl radical or a chlorine atom, with the proviso that if R_3' represents a lower alkyl radical, R_1' and R_3' together contain at least 3 carbon atoms.

4. A lower alkyl-3-O- R_3'' -5,6-di-O-R-D-glucofuranoside, wherein R_3'' represents a hydrogen atom or a lower alkyl group, and R represents a benzyl radical which is optionally substituted by halogen atoms, with the proviso that if R_3'' represents a lower alkyl radical, the latter together with the lower alkyl radical of the substituent in the 1-position contains at least 3 carbon atoms and a 2-O-succinyl compound thereof.

5. A lower alkyl-3-O- R_3'' -5,6-di-O-R-D-glucofuranoside, wherein R_3'' represents a hydrogen atom or a lower alkyl group, and R represents a benzyl radical which is optionally substituted by chlorine atoms, with the proviso that if R_3'' represents a lower alkyl radical, the latter together with the lower alkyl radical of the substituent in the 1-position contains at least 3 carbon atoms, and a 2-O-succinyl compound thereof.

6. Ethyl-3-O-methyl-5,6-di-O-benzyl-D-glucofuranoside.

7. The α -anomer of the compound claimed in claim 6.8. The β -anomer of the compound claimed in claim 6.9. *Sec*-Butyl-3-O-methyl-5,6-di-O-benzyl-D-glucofuranoside.

10. Ethyl-3-O-methyl-5,6-di-O-(4-methylbenzyl)-D-glucofuranoside.

11. Ethyl-3-O-methyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside.

12. Ethyl-3-O-allyl-5,6-di-O-benzyl-D-glucofuranoside.

13. Ethyl-3-O-n-propyl-5,6-di-O-benzyl-D-glucofuranoside.

14. Ethyl-3-O-n-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside.

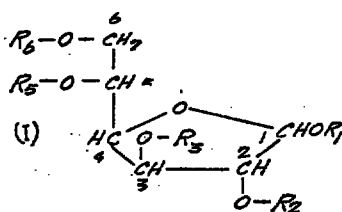
15. The α -anomer of the compound claimed in claim 14.16. The β -anomer of the compound claimed in claim 14.

17. Ethyl-3-O-allyl-5,6-di-O-(4-methylbenzyl)-D-glucofuranoside.

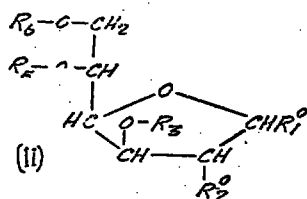
18. Ethyl-5,6-di-O-benzyl-D-glucofuranoside.



19. *n*-Butyl-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside.
20. *n*-Butyl-3-O-methyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside.
21. Ethyl-2-O-(β -carboxy-propionyl)-3-O-methyl-5,6-di-O-benzyl-D-glucofuranoside.
22. Ethyl-2-O-(β -carboxy-propionyl)-3-O-*n*-propyl-5,6-di-O-(4-chlorobenzyl)-D-glucofuranoside.
23. Ethyl-2-O-(β -carboxy-propionyl)-3-O-*n*-propyl-5,6-di-O-benzyl-D-glucofuranoside.
24. A salt of a compound claimed in any one of claims 1—4 and 21—23, which is capable of salt formation.
25. A physiologically tolerable salt of a compound claimed in any one of claims 1—4 and 21—23 which is capable of salt formation.
26. A physiologically tolerable ammonium, alkali metal or alkaline earth metal salt of a compound claimed in any one of claims 1—4 and 21—23 which contains a free carboxyl group.
27. A pharmaceutical preparation comprising a compound as claimed in any one of claims 1—23, 25 and 26 in conjunction or admixture with a pharmaceutically suitable carrier.
28. A pharmaceutical preparation substantially as described in Example 17.
29. A process for the manufacture of a D-glucofuranoside of formula



wherein R_1 represents a lower aliphatic hydrocarbon radical which optionally carries hydroxyl or lower alkoxy groups, a cycloaliphatic hydrocarbon radical which optionally carries lower alkyl groups, or a benzyl radical which is optionally substituted in the phenyl ring, R_2 represents a hydrogen atom or the acyl radical of an organic carboxylic acid, R_3 represents a hydrogen atom or a lower aliphatic hydrocarbon radical, and R_4 and R_5 each represents a benzyl radical which is optionally substituted in the phenyl ring, with the proviso that if R_3 represents a lower aliphatic hydrocarbon radical, the groups represented by R_1 and R_3 together contain at least 3 carbon atoms, and a salt of a compound of the above type capable of salt formation, wherein a D-glucofuranose of formula II



wherein R_3 , R_4 and R_5 have the meanings given above and wherein R_1° represents a hydroxyl group and R_2° a hydroxyl group or an acyloxy radical, wherein acyl denotes the radical of an organic carboxylic acid, or R_1° and R_2° together represent the grouping of formula $-\text{O}-\text{X}-\text{O}-$, wherein X represents an optionally substituted methylene group, is reacted with a compound of formula $R_1-\text{OH}$ (R_1 having the meaning given above) in the presence of an acid, or a D-glucofuranose of formula II, in which R_3 , R_4 and R_5 have their above meanings and in which R_1° represents a reactive esterified hydroxyl group and R_2° represents an acyloxy radical, wherein acyl denotes the acyl radical of an organic carboxylic acid, is reacted with a compound of the formula $R_1-\text{OH}$ in the presence of an acid acceptor, and, if desired, an unsaturated lower aliphatic hydrocarbon radical in a resulting compound is saturated and/or, if desired, an acyloxy radical in the 2-position in a resulting compound is converted into a free hydroxyl group and/or, if desired, a free hydroxyl group in the 2-position in a result-



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ing compound is converted into a hydroxyl group esterified by an organic carboxylic acid and/or, if desired, a resulting compound capable of salt formation is converted into a salt or a resulting salt into the free compound and/or, if desired, a resulting anomer mixture is split into the individual anomers.

- 5 30. A process for the manufacture of a D-glucofuranoside of formula I shown in claim 29, wherein a D-glucofuranose of formula II shown in claim 29, in which R_3 , R_5 and R_6 have the meanings given in claim 29 and in which R_1° and R_2° together represent the grouping of formula $-O-X-O-$, wherein X represents an optionally substituted methylene group, is reacted with a compound of formula R_1-OH (R_1 having the meaning given in claim 29) in the presence of an acid, or a D-glucofuranose of formula II, wherein R_3 , R_5 and R_6 have the meanings given in claim 29 and R_1° represents a reactive esterified hydroxyl group and R_2° represents an acyloxy radical, wherein acyl denotes the acyl radical of an organic carboxylic acid, is reacted with a compound of formula R_1-OH (R_1 having the meaning given in claim 29) in the presence of a metal derivative thereof, and, if desired, an unsaturated lower aliphatic hydrocarbon radical in a resulting compound is saturated, and/or, if desired, an acyloxy radical in the 2-position in a resulting compound is converted into a free hydroxyl group, and/or, if desired, a free hydroxyl group in the 2-position in a resulting compound is converted into a hydroxyl group esterified by an organic carboxylic acid, and/or, if desired, a resulting compound capable of salt-formation is converted into a salt or a resulting salt into the free compound, and/or, if desired, a resulting anomer mixture is resolved into the individual anomers.
- 10 31. A process as claimed in claim 29, wherein X represents an unsubstituted, monosubstituted or disubstituted methylene group.
- 15 32. A process as claimed in claim 30, wherein X represents an unsubstituted, monosubstituted or disubstituted methylene group.
- 20 33. A process as claimed in claim 31, wherein substituents of the methylene group are optionally substituted monovalent or bivalent aliphatic hydrocarbon radicals.
- 25 34. A process as claimed in claim 32, wherein substituents of the methylene group are optionally substituted monovalent or bivalent aliphatic hydrocarbon radicals.
- 30 35. A process as claimed in either one of claims 31 and 33, wherein substituents of the methylene group are lower alkyl groups.
- 35 36. A process as claimed in either one of claims 32 and 34, wherein substituents of the methylene group are lower alkyl groups.
- 40 37. A process as claimed in any one of claims 31 and 33, wherein the substituents of the methylene group are methyl groups.
- 45 38. A process as claimed in any one of claims 32 and 34, wherein the substituents of the methylene group are methyl groups.
- 50 39. A process as claimed in claim 31, wherein substituents of the methylene group are optionally substituted aromatic radicals.
- 55 40. A process as claimed in claim 32, wherein substituents of the methylene group are optionally substituted aromatic radicals.
- 60 41. A process as claimed in claim 31, wherein substituents of the methylene group are optionally functionally converted carboxyl groups.
42. A process as claimed in claim 32, wherein substituents of the methylene group are optionally functionally converted carboxyl groups.
43. A process as claimed in any one of claims 29, 31, 33, 35, 37, 39 and 41, wherein the acid used is an inorganic acid.
44. A process as claimed in any one of claims 30, 32, 34, 36, 38, 40 and 42, wherein the acid used is an inorganic acid.
45. A process as claimed in claim 43, wherein the acid used is hydrochloric acid.
46. A process as claimed in claim 44, wherein the acid used is hydrochloric acid.
47. A process as claimed in any one of claims 29, 31, 33, 35, 37, 39, 41, 43, and 45, wherein the alcoholic reagent represented by R_1-OH is used as the solvent (R_1 having the meaning given in claim 29).
48. A process as claimed in any one of claims 30, 32, 34, 36, 38, 40, 42, 44 and 46, wherein the alcoholic reagent represented by R_1-OH is used as the solvent (R_1 having the meaning given in claim 29).
49. A process as claimed in any one of claims 29, 43, 45 and 47, wherein the reaction of the starting material of formula II, shown in claim 29, wherein R_3 , R_5 and R_6 have the meanings given in claim 29 and R_1° represents a free hydroxyl group and R_2° a free hydroxyl group or an acyloxy radical, with the alcohol of formula R_1-OH (R_1 having the meaning given in claim 29) is carried out at a mineral acid concentration of 0.05N to 1N.



50. A process as claimed in claim 49, wherein the mineral acid concentration is 0.1N to 0.5N.
51. A process as claimed in claim 29, wherein R_1^o represents a halogen atom.
52. A process as claimed in claim 30, wherein R_1^o represents a halogen atom.
53. A process as claimed in claim 29, wherein R_1^o represents a bromine atom.
54. A process as claimed in claim 30, wherein R_1^o represents a bromine atom.
55. A process as claimed in claim 29, wherein the acid-binding reagent is a silver, lead or mercury salt or a corresponding oxide, a tertiary base or a metal derivative of a compound of formula R_1-OH , R_1 having the meaning given in claim 1.
56. A process as claimed in claim 55, wherein the metal derivative of a compound of formula R_1-OH is an alkali metal, alkaline earth metal or silver derivative.
57. A process as claimed in any one of claims 30, 52 and 54, wherein the metal derivative of a compound of formula R_1-OH is an alkali metal, alkaline earth metal or silver derivative.

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